Drug allergy

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Drug allergy is one type of adverse reaction to drugs and encompasses a spectrum of hypersensitivity reactions with heterogeneous mechanisms and clinical presentations. A thorough history is essential to the management of drug allergy. Laboratory testing has a very limited role in the management of drug allergy. Graded dose challenges and procedures to induce drug tolerance might be required in patients with drug allergy when there is a definite need for a particular agent. Management of reactions to specific agents, including β-lactam antibiotics, sulfonamides, local anesthetics, radiocontrast media, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and biologic modifiers, will be discussed in further detail. (J Allergy Clin Immunol 2010;125:S126-37.)

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Abbreviations used

ACE-I:	Angiotensin-converting enzyme inhibitor
ADR:	Adverse drug reaction
AERD:	Aspirin-exacerbated respiratory disease
ASA:	Acetylsalicylic acid
DILE:	Drug-induced lupus erythematosus
DRESS:	Drug rash with eosinophilia and systemic symptoms
NSAID:	Nonsteroidal anti-inflammatory drug
NSF:	Nephrogenic systemic fibrosis
PPL:	Penicilloyl-polylysine
RCM:	Radiocontrast media
SJS:	Stevens-Johnson syndrome
TEN:	Toxic epidermal necrolysis
TMP-SMX:	Trimethoprim-sulfamethoxazole

EPIDEMIOLOGY AND CLASSIFICATION OF ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment. ADRs are commonly encountered in both inpatient and outpatient settings. In a meta-analysis of inpatient ADR prospective studies, 15.1% of patients sustained ADRs during their hospitalizations, and 6.7% of patients experienced serious ADRs.[1] In a 4-week prospective cohort study of outpatients followed in primary care clinics, 25% of patients reported ADRs, 13% of which were serious.[2]

ADRs are categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reactions are usually dose dependent, related to the known pharmacologic actions of the drug, and occur in otherwise healthy subjects. Predictable reactions account for about 80% of all ADRs and are subdivided into overdose, side effects, secondary effects, and drug interactions. Unpredictable reactions are generally dose independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible subjects. Unpredictable reactions are subdivided into drug intolerance (an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug), drug idiosyncrasy (abnormal and unexpected effect, usually caused by underlying abnormalities of metabolism, excretion, or bioavailability), drug allergy (immunologically mediated ADRs [including IgE-mediated drug allergy]), and pseudoallergic reactions (also called anaphylactoid reactions, which are due to direct release of mediators from mast cells and basophils rather than IgE antibodies).

The Gell and Coombs system of hypersensitivity is the most common method of classifying immunologically mediated ADRs. It is comprised of immediate-type reactions mediated by drug-specific IgE antibodies (type I), cytotoxic reactions mediated by drug-specific IgG or IgM antibodies (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV). Type IV reactions can be subdivided into 4 categories involving activation and recruitment of monocytes (type IVa), eosinophils (type IVb), $CD4^+$ or $CD8^+$ T cells (type IVc), and neutrophils (type IVd).[3]

The pharmacologic interaction with immune receptors concept is a recently proposed addition to drug hypersensitivity classification. In this scheme a drug binds noncovalently to a T-cell receptor, which can lead to an immune response through interaction with an MHC receptor. In this scenario no sensitization is required because there is direct stimulation of memory and effector T cells analogous to the concept of superantigens.[4] Although these mechanistic classifications of drug-induced allergic reactions are useful, not all drug-induced allergic reactions can be categorized based on these limited mechanisms of hypersensitivity.

CLINICAL MANIFESTATIONS OF IMMUNOLOGICALLY MEDIATED ADRS

Drug-induced allergic reactions can affect numerous organ systems and manifest in a variety of reactions, including various drug-induced allergic syndromes, and many drug-induced allergic reactions can have more than 1 mechanistic pathway (Table I).

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TABLE I. Heterogeneity of drug-induced allergic reactions

Organ-specific reactions	Clinical features	Examples of causative agents
Cutaneous		
Exanthems	Diffuse fine macules and papules Evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β-lactam antibiotics Bradykinin mediated: ACE-I
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
Pustules	Acneiform Acute generalized eczematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium-channel blockers, ACE-Is
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalacylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
Multiorgan reactions		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, mAbs
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

Cutaneous manifestations are the most common physical manifestation of drug-induced allergic reactions; however, many other organ systems can be involved, including hematologic abnormalities, hepatitis, pneumonitis, lymphadenopathy, or arthralgias. Although drug-induced allergic reactions might present with noncutaneous physical findings, these findings are generally nonspecific and are not nearly as helpful in diagnosis and management decisions. Numerous cutaneous eruptions have been attributed to drug-induced allergic reactions and have been reviewed elsewhere.[5]

Because certain drug eruptions are associated with specific immunologic reactions, it is important to characterize the type of eruption in regard to determining the cause, further diagnostic tests, and management decisions. The most common cutaneous manifestation of drug-induced allergic reactions is a generalized exanthem (also know as a maculopapular eruption). Urticaria, angioedema, or both is another common cutaneous drug reaction that can be due to IgE-mediated reactions, serum sickness, pseudoallergic reactions, or other mechanisms (eg, bradykinin mediated). The most severe form of cutaneous drug reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is another cutaneous, drug-induced, multiorgan inflammatory response that can be life-threatening. First described in conjunction with anticonvulsants, it has since been ascribed to a variety of other drugs. DRESS is atypical from other drug-induced allergic reactions in that the reaction develops later, usually 2 to 8 weeks after therapy is started; symptoms can worsen after the drug is discontinued; and symptoms can persist for weeks or even months after the drug has been discontinued.[6]

EVALUATION: HISTORY TAKING

A thorough history is an essential component in the evaluation of patients with suspected drug allergies. The history helps guide the clinician in the choice of diagnostic tests and whether it might be safe to reintroduce the medication. If possible, the original medical record that describes the drug reaction should be reviewed. The most important components of a drug allergy history are as follows.

- *What is the name of the medication?* Although obvious, not uncommonly, patients are unable to provide this basic piece of information. Reasons for this include passage of time and the fact that names of many medications sound similar, and patients who reacted to multiple drugs might confuse which drug caused which reaction.
- *How long ago did the reaction occur?* The time elapsed is important because some allergies, such as to penicillin, wane over time.

- *Which systems (eg, cutaneous, respiratory, and gastrointestinal) were involved in the reaction, and what were the characteristics?* If a cutaneous eruption occurred, what kind was it (eg, urticarial, morbilliform, bullous, or exfoliative)? Showing the patient pictures of different types of rashes might be helpful.
- *When during the course did the reaction occur?* Alternatively, was the onset of symptoms after the course was completed?
- *Why was the medication prescribed?* The indication is important because symptoms of the underlying disease might be misattributed to the medication (eg, a truncal rash during penicillin therapy for streptococcal pharyngitis).
- *Was the patient taking concurrent medications at the time of the reaction?* Antibiotics are usually blamed for reactions, but drugs such as opiates and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently coadministered and might be responsible instead.
- *What was the therapeutic management required secondary to the reaction?* Self-discontinuation of a medication suggests a milder reaction than if a patient required hospitalization. Some patients recall treatment they received more readily than the characteristics of the reaction itself.
- *Had the patient taken the same or a cross-reacting medication before the reaction?* Most allergic reactions require a period of sensitization, typically during a previous course that was tolerated.
- *Has the patient been exposed to the same or similar medication since the reaction?* For instance, some patients with a history of penicillin allergy report that later they tolerated a course of amoxicillin clavulanate (Augmentin; GlaxoSmithKline, London, United Kingdom), not realizing the latter is a penicillin-class compound.
- *Has the patient experienced symptoms similar to the reaction in the absence of drug treatment?* The most common situation is chronic recurrent idiopathic urticaria, which can be confused for drug allergy.
- *Does the patient have an underlying condition that favors reactions to certain medications?* Examples of such conditions include mononucleosis for ampicillin reactions and HIV infection for trimethoprim-sulfamethoxazole (TMP-SMX) reactions.

DIFFERENTIAL DIAGNOSIS IN DRUG ALLERGY

Drug-induced allergic reactions can present in numerous ways, affecting single organs or with multiorgan involvement. However, each clinical presentation is not unique or specific to drug-induced allergic reactions, and therefore other conditions might need to be considered based on the presentation. For example, a morbilliform eruption occurring in a child receiving amoxicillin for an upper respiratory tract infection might indeed be due to a viral exanthem and not a drug-induced allergic reaction. In addition, patients with multiple drug allergies might actually have an underlying chronic disease and are inappropriately labeled with multiple drug allergies. This frequently occurs in patients with underlying chronic urticaria or anxiety disorders but can also occur with other conditions, such as asthma, vocal cord dysfunction, idiopathic anaphylaxis, or rarely even mastocytosis.

LABORATORIES IN DRUG ALLERGY

Routine laboratory evaluation appropriate to the clinical setting might be useful for the evaluation of a patient with a suspected drug reaction, depending on the history and physical examination findings. Although eosinophilia is often suggestive of a drug-induced allergic reaction, most patients with drug-induced allergic reactions do not have eosinophilia, and therefore the absence of eosinophilia clearly does not exclude a drug-induced allergic cause. Autoantibodies might be helpful in the evaluation of drug-induced vasculitis (eg, antinuclear cytoplasmic antibody) and drug-induced lupus erythematosus (DILE). In the case of systemic DILE, antihistone antibody levels are frequently positive, whereas in patients with cutaneous DILE, anti-Ro/SSA, anti-La/SSB, or both levels are frequently positive.[7]

In cases of suspect anaphylaxis, a diagnosis of anaphylaxis might be made by detecting an increase in serum total tryptase levels above baseline values or in serum mature tryptase (also known as β-tryptase) levels, which peak 0.5 to 2 hours after drug administration and then decrease with a half-life of about 2 hours.[8] Additional methods for detecting systemic mast cell mediator release include obtaining 24-hour urine collections for major urinary metabolites of histamine or prostaglandin D_2.

For immediate hypersensitivity reactions mediated by IgE antibodies, demonstration of the presence of drug-specific IgE is usually taken as sufficient evidence that the patients is at significant risk of having a type I reaction if the drug is administered. This is helpful in the case of high-molecular-weight agents. In the case of small-molecular-weight drugs, validated and reliable skin test reagents are only available for penicillin. Haptenation of the β-lactam ring of penicillin to a protein (eg, penicilloyl-polylysine [PPL]) enhances the immunogenicity, with resultant improvement in the detection of specific IgE. The negative predictive value of penicillin skin testing (with PPL, penicillin G, and penicilloate and/or penilloate) for serious immediate-type reactions approaches 100%. However, insufficient knowledge about drug degradation products, metabolites, or both and how they are conjugated with body proteins has been an impediment to developing either skin or *in vitro* assays for assessing immune responses to most other small-molecular-weight drug chemicals. Specific IgE *in vitro* assays (eg, RASTs, ImmunoCAP, and Immulite) are available, although most are not adequately validated with unclear specificity and sensitivity and lack internal positive controls. In addition, *in vitro* assays for IgE to drugs are hampered because of difficulties with binding of drug allergens to solid-phase matrices.

The basophil activation test is a recently described method of evaluating expression of CD63 or CD203C on basophils after stimulation with an allergen. There are very limited data using this method to evaluate patients with possible drug allergies to β-lactam antibiotics, NSAIDs, and muscle relaxants,[9] and further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool. Drug patch testing might be useful for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions, but generally is not helpful for SJS or urticarial eruptions.[10] In complex cases in which multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy might be useful. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy might not definitively exclude alternative causes.

TABLE II. Induction of drug tolerance procedures

Type of drug tolerance	Duration	Initial dose	Mechanisms	Example
Immunologic IgE (drug desensitization)	Hours	μg	Antigen-specific mediator depletion, downregulation of receptors	Penicillin Carboplatin, cisplatin, oxaliplatin
Immunologic non-IgE	Hours to days	mg	Unknown	TMP-SMX
Pharmacologic	Hours to days	mg	Metabolic shift, internalization of receptors	Aspirin
Nonimmunologic mast cell activation	Hours	μg	Unknown	Paclitaxel
Undefined	Weeks	μg-mg	Unknown	Allopurinol

INDUCTION OF DRUG TOLERANCE AND GRADED CHALLENGE PROCEDURES

In situations in which there is a definite medical need for a particular agent, no suitable alternative agent exists, and testing with high negative predictive value does not exist, there are primarily 2 options for the patient with a drug allergy. On the one hand, a procedure to induce temporary drug tolerance can be performed to allow the patient to take the drug safely. In contrast, a test dose or graded challenge can be administered to determine whether the patient is currently allergic to the particular drug.

The term *drug desensitizatio*n has been widely used and is defined as a procedure that modifies a patient's immune response to a drug, allowing him or her to take the drug temporarily in a safe manner. In cases such as IgE-mediated drug allergy (eg, to penicillin), the term drug desensitization is accurate in that patients are indeed sensitized to penicillin before the procedure and afterward typically have diminished or absent skin test reactions and hence are less sensitive or desensitized.[11] However, the term drug desensitization has also been used to describe a number of different protocols for patients with non–IgE-mediated drug allergies who in many cases are not truly sensitized initially but might react to the drug through various non–IgE-mediated or even nonimmune mechanisms. Recently, the term *induction of drug tolerance* has been proposed as a more appropriate term to encompass not only IgE-mediated desensitization procedures but other non–IgE-mediated desensitizations as well.[12] The term *drug tolerance* is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunologic tolerance. Drug desensitizations for IgE-mediated drug allergy are indeed a form of immunologic drug tolerance. Induction of drug tolerance procedures modify a patient's response to a drug (through immunologic or other nonimmunologic mechanisms) to temporarily allow treatment with it safely. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms (Table II).

All procedures to induce drug tolerance involve administration of incremental doses of the drug but vary considerably over the starting dose and duration of the procedure. Through various mechanisms, these procedures induce a temporary state of tolerance to the drug, which is maintained only as long as the patient continues to take the specific drug. Therefore this procedure would need to be repeated in the future if a patient requires the drug again after finishing a prior therapeutic course.

Graded challenge, or test dosing, is defined as a procedure to determine whether a patient will have an adverse reaction to a particular drug by administering lower than therapeutic doses over a period of time with observation for reactions. The rationale for starting with a lower dose is based on the concept that a smaller dose of allergen will result in a less severe and more easily treated reaction. Unlike induction of drug tolerance procedures, a graded challenge does not modify a patient's immunologic or nonimmunologic response to a given drug. Although it is not possible to be absolutely certain that a patient is not allergic to a drug because valid diagnostic tests are not available for most drugs, graded challenges are intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug. Furthermore, the benefit of treatment with the drug should outweigh the risk of performing the graded challenge. The starting dose for graded challenge is generally higher than for induction of drug tolerance procedures, and the number of steps in the procedure might be 2 or several. The time intervals between doses are dependent on the type of previous reaction, and the entire procedure can take hours or days to complete. After a successful graded challenge and therapeutic course of the drug, future courses of the drug can be started without another challenge.

A typically safe starting dose for an IgE immune induction of drug tolerance (desensitization) procedure is about twice the dose used in the puncture or intradermal skin test used to document the IgE-mediated allergy. A typical starting dose for a graded challenge is 1/100th of the final treatment dose. This is in contrast to the starting dose for an IgE immune induction of drug tolerance, in which case the starting dose is often 1/10,000th of the final dose. Caution should be exercised when a graded challenge consisting of more than 4 or 5 steps is performed because it might inadvertently induce modifications of immune effector cells and therefore induce drug tolerance in the patient. In these circumstances future administrations of the drug should be made cautiously.

The choice of whether to introduce a clinically indicated drug through a graded challenge or through induction of drug tolerance mainly depends on the likelihood that the patient is allergic at the time of the procedure. Patients who, based on their history, diagnostic test results, or both, are unlikely to be allergic to a drug can undergo graded challenge. For example, if penicillin skin testing is unavailable and a patient with a history of a mild pruritic rash during penicillin treatment 20 years ago requires penicillin therapy, it would be reasonable to administer penicillin through a graded oral challenge. Patients who have a relatively higher likelihood of being allergic to a drug should undergo an induction of drug tolerance procedure. For example, if penicillin skin testing is unavailable and a patient with a recent history of penicillin-induced anaphylaxis requires penicillin, it should be administered through induction of drug tolerance. Graded challenge (or induction of drug tolerance) should almost never be performed if the reaction history is consistent with a severe non–IgE-mediated reaction, such as SJS, TEN, DRESS, hepatitis, or hemolytic anemia.

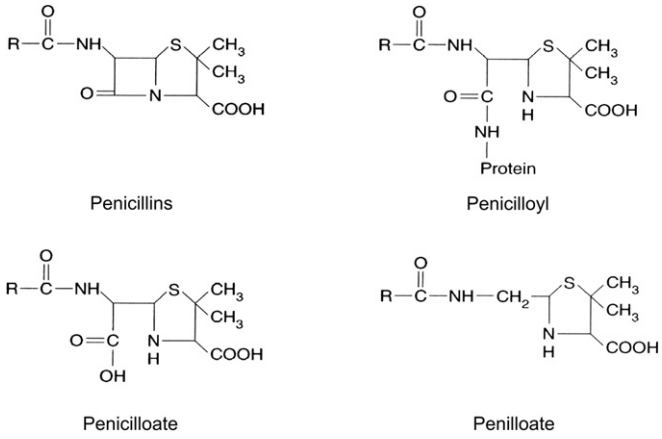

FIG 1. Chemical structures of major and minor penicillin allergenic determinants. The R-group distinguishes different penicillin compounds.

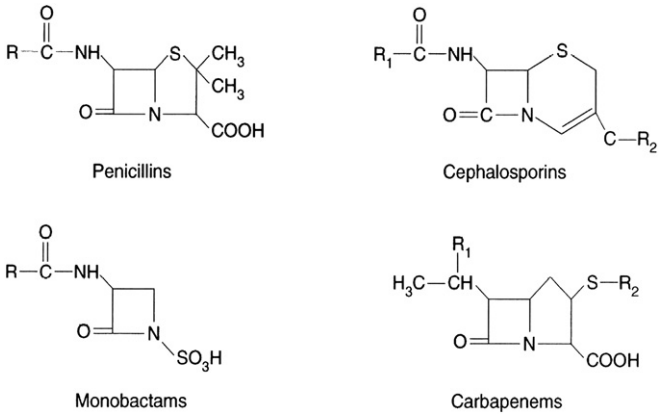

FIG 2. Chemical structures of β-lactam antibiotics.

MANAGEMENT OF COMMON ALLERGIC REACTIONS TO SPECIFIC AGENTS

β-Lactam antibiotics: Penicillins

Penicillin is the most prevalent medication allergy, with about 10% of patients reporting being allergic. When evaluated, however, approximately 90% of patients with a history of penicillin allergy are able to tolerate penicillins.[13,14] This observation is partly due to the fact that penicillin-specific IgE antibodies wane over time and many (but not all) patients outgrow their penicillin allergy. In addition, many patients were probably mislabeled as being allergic at the time of their reaction because symptoms and signs of an underlying illness can be confused for a penicillin-induced reaction. Patients labeled as allergic to penicillin are more likely to be treated with more expensive and broad-spectrum antibiotics (eg, quinolones and vancomycin),[15] which contributes to the development and spread of multiple drug-resistant bacteria and leads to higher health care costs.

The immunochemistry of penicillin was elucidated in the 1960s.[16] Under physiologic conditions, penicillin spontaneously degrades to a number of reactive intermediates that act as haptens and covalently bind to self-proteins, which then can elicit an immune response. Approximately 95% of penicillin degrades to the penicilloyl moiety, which is referred to as the major antigenic determinant (Fig 1). The remaining portion of penicillin degrades to several derivatives, and of these, penicilloate and penilloate are the most important to induce allergic responses. These 2 compounds, along with penicillin itself, are collectively known as the minor antigenic determinants, and they cover all clinically relevant allergenic determinants not covered by penicilloyl.

Less commonly, the R-group side chain, which distinguishes different penicillin compounds, can also serve as an allergenic determinant (Fig 2). This type of allergy results in patients who selectively react to amoxicillin, for example, but are able to tolerate other penicillins.[17] In contrast, patients allergic to the core β-lactam portion of penicillin cross-react to various penicillins. Selective allergy to amoxicillin or ampicillin is relatively common in parts of Southern Europe and quite infrequent in the United States; the reason for these differences in unknown.

Insight into the immunochemistry of penicillin has allowed for the development of validated skin test reagents to detect penicillin-specific IgE antibodies.[13,14] PPL was commercially available as Pre Pen from 1974 until 2004 and is expected to return to the market in 2009. Of the minor determinants, only penicillin G is commercially available. Some medical centers synthesize penicilloate and penilloate for local use. Amoxicillin or ampicillin should be included in the skin-testing panel when patients report reactions to these antibiotics.

The negative predictive value of penicillin skin testing is very high. In large-scale studies 1% to 3% of patients with negative skin test responses (with both major and minor determinants) had mild and self-limiting reactions on being challenged with the drug.[13,14] Some studies report that about 10% to 20% of patients with penicillin allergy have skin test reactivity only to penicilloate or penilloate.[13,14,18] The clinical significance of these findings is uncertain. Penicillin challenges of subjects with negative skin test responses to PPL and penicillin G[19] have similar reaction rates compared with those in subjects with negative skin test responses to the full set of major and minor penicillin determinants.[13,14]

Reaction history is a poor predictor of who will demonstrate a positive penicillin skin test response. Overall, about one third of patients with positive penicillin skin test responses report vague reaction histories.[20] Therefore any patient with a history of a possible IgE-mediated reaction to penicillin is a candidate for skin testing. Elective skin testing (when patients are well and not in immediate need of antibiotic therapy) should be considered. The medical care of patients labeled as having penicillin allergy can be compromised because of use of inappropriate antibiotics.[15] Patients who have positive responses should receive penicillins only through an induction of drug tolerance procedure. For patients with negative skin test responses, clinicians should consider a challenge with penicillin because without it, many patients are subsequently not treated with β-lactams because of fear on either the part of the patient or treating physician.

Resensitization after oral treatment with penicillin is rare in both pediatric and adult patients, including after repeated courses.[21,22] Hence routine repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated 1 or more courses of oral penicillin. Consideration can be given to retesting individuals with recent or particularly severe previous reactions. Resensitization after high-dose parenteral treatment with penicillin might be more likely, but data are limited. Nevertheless, repeat penicillin skin testing in this situation might be warranted.[23]

TABLE III. Summary of studies of cephalosporin challenges in patients with a history of penicillin allergy without preceding penicillin allergy testing

Reference	History of penicillin allergy	No history of penicillin allergy	Cephalosporins administered
Dash, 1975[E1]	25/324 (7.7%)	140/17,216 (0.8%)	Cephalexin and cephaloridine
Petz, 1978[E2]	57/701 (8.1%)	285/15,007 (1.9%)	Cephalexin, cephaloridine, cephalothin, cefazolin, and cefamandole
Goodman et al, 2001[E3]	1/300 (0.3%)	1/2,431 (0.04%)	Cefazolin (in all but 1 patient)
Daulat et al, 2004[E4]	1/606 (0.17%)	15/22,664 (0.07%)	First generation (42%), second generation (21%), third/fourth generations (37%)
Fonacier et al, 2005[E5]	7/83 (8.4%)	Not reported	First generation (59%), second generation (8.4%), third generation (25%), fourth generation (7%)

Please see the Online Repository at www.jacionline.org for complete reference citations.

Without penicillin skin testing, the approach to patients with a history of penicillin allergy is based on the reaction history and likelihood of needing treatment with penicillins. Patients with a low likelihood of being allergic (eg, those with distant [> 10 years] or vague reaction histories) might receive penicillins through cautious graded challenge. On the other hand, patients with severe reaction histories (eg, anaphylaxis) or recent reactions should receive penicillins only through an induction of drug tolerance procedure.

β-Lactam antibiotics: Penicillin/cephalosporin cross-reactivity

Retrospective studies of administration of cephalosporins to patients with a history of penicillin allergy, without prior penicillin skin testing, showed much higher reaction rates in the 1970s compared to recently (Table III). Before 1980, cephalosporins were contaminated with trace amounts of penicillin, which would overestimate the cross-reactivity. Studies that rely on patient history to diagnose penicillin allergy are problematic because about 90% of these patients do not have penicillin allergy at the time of treatment with cephalosporins. Furthermore, some patients with severe penicillin reaction histories might have been denied treatment with cephalosporins.

Table IV summarizes studies in which patients with positive penicillin skin test responses were challenged with cephalosporins. Although these studies are of higher quality by virtue of proving type I penicillin sensitization before cephalosporin challenge, they still have limitations, including lack of control groups (eg, patients challenged with placebo or challenged with non–β-lactam antibiotics) and the fact that the challenges were not blinded. Patients might have an underlying propensity to react to unrelated drugs,[24] which can account for some reactions to cephalosporins in patients with penicillin allergy. In patients with documented allergic-like reactions to penicillins, the relative risk for allergic-like reactions was increased for both cephalosporins and sulfonamides.[25]

Ideally, management of cephalosporin administration to patients with a history of penicillin allergy includes penicillin skin testing (when available). About 90% of patients have negative penicillin skin test responses and can safely receive cephalosporins (as well as other β-lactams). Patients with positive penicillin skin test responses have a slightly increased risk of reacting to cephalosporins, and therefore they should be administered through graded challenge or an induction of tolerance procedure. When penicillin skin testing is not available, cephalosporins might be given through a full-dose or graded challenge, depending on the reaction history and the likelihood the patient has penicillin allergy. The reaction risk is very low, but rarely, anaphylactic reactions have been described.

Allergic cross-reactivity between amoxicillin and cephalosporins that share identical R-group side chains is higher than for patients with positive penicillin skin test responses. Twelve percent to 38% of patients proved to be selectively allergic to amoxicillin (ie, able to tolerate penicillin) reacted to cefadroxil.[26,27] Therefore patients with amoxicillin allergy should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, and cefatrizine) or receive them through induction of drug tolerance procedures. Similarly, patients with ampicillin allergy should avoid cephalexin, cefaclor, cephradine, cephaloglycin, and loracarbef or receive them through induction of drug tolerance procedures.

β-Lactam antibiotics: Penicillin/carbapenem cross-reactivity

Data on allergic cross-reactivity between penicillin and carbapenems are similar to those for penicillin/cephalosporins. Table V summarizes retrospective studies of carbapenem administration to patients with a history of penicillin allergy (no penicillin skin testing performed). The carbapenem reaction rate is somewhat higher in patients with a history of penicillin allergy. Table V also summarizes studies in which patients with positive penicillin skin test responses were challenged with carbapenems, and no patients experienced reactions (3 patients were not challenged because of positive carbapenem skin test responses).

The approach to carbapenem administration in patients with a history of penicillin allergy is analogous to that for cephalosporins. Patients with negative penicillin skin test responses can receive carbapenems safely. Patients with positive penicillin skin test responses should receive carbapenems through graded challenge, given that the chance of reacting is less than 1%. Without penicillin skin testing, carbapenems can be administered through graded challenge. Skin testing with carbapenems can be considered in patients with positive penicillin skin test responses or when penicillin skin testing is not performed.

Sulfonamides

Sulfonamides are defined as drugs with an SO_2-NH_2 moiety. Sulfonamide antibiotics also contain an aromatic amine at the N_4 position and a substituted ring at the N_1 position, whereas nonantibiotic sulfonamides do not. Beside penicillins, sulfonamide

TABLE IV. Summary of patients with positive penicillin skin test responses challenged with cephalosporins, not including patients with positive skin test responses to only amoxicillin or ampicillin (and not to major, minor, or both penicillin determinants)

	Cephalosporin			
Reference	No. of patients	No. of reactions	Skin testing	Comment
Girard, 1968[E6]	23	2 (8.7%)	No	Both reactions to cephaloridine
Assem and Vickers, 1974[E7]	3	3 (100%)	No	All reactions to cephaloridine
Warrington et al, 1978[E8]	3	0	Yes	
Solley et al, 1982[E9]	27	0	No	
Saxon et al, 1987[E10]	62	1 (1.6%)	No	Cephalosporin not noted
Blanca et al, 1989)[E11]	16	2 (12.5%)	No	Both reactions to cefamandole
Shepherd and Burton, 1993[E12]	9	0	No	
Audicana et al, 1994[E13]	12	0	Yes	
Pichichero and Pichichero, 1998[E14]	39	2 (5.1%)	No	Reaction to cefaclor and ?
Novalbos et al, 2001[E15]	23	0	Yes	
Macy and Burchette, 2002[E16]	42	1 (2.4%)	No	Reaction to cefixime
Romano et al, 2004[E17]	75	0	Yes	
Greenberger and Klemens, 2005[E18]	6	0	No	
Park et al, 2006[E19]	37	2 (5.4%)	No	Cephalosporins not noted

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TABLE V. Summary of carbapenem challenges in patients with a history of penicillin allergy without preceding penicillin allergy testing and in patients with positive penicillin skin test responses

	Carbapenem reaction rate			
Reference	History of penicillin allergy (no penicillin ST)	No history of penicillin allergy	History of penicillin allergy (+ penicillin ST)	*P* value
McConnell et al, 2000[E20]	4/63 (6.3%)	NA	NA	NA
Prescott et al, 2004[E21]	11/100 (11%)	3/111 (2.7%)	NA	.024
Sodhi et al, 2004[E22]	15/163 (9.2%)	4/103 (3.9)	NA	.164
Cunha et al, 2008[E23]	0/110 (0%)	NA	NA	NA
Romano et al, 2006[E24]	NA	NA	0/110*	NA
Romano et al, 2007[E25]	NA	NA	0/103*	NA
Atanaskovic et al, 2008[E26]	NA	NA	0/107*	NA

Please see the Online Repository at www.jacionline.org for complete reference citations.
ST, Skin test response.

antibiotics are the most common cause of drug-induced allergic reactions.[28] They most commonly cause delayed cutaneous maculopapular/morbilliform eruptions, and IgE-mediated reactions are relatively infrequent. Sulfonamides are by far the most common cause of SJS and TEN.[29]

Patients infected with HIV have a greatly increased risk of cutaneous reactions from sulfonamide antibiotics, which is probably related to immunologic factors and frequent exposure to these antibiotics. The typical reaction to TMP-SMX in HIV-positive patients consists of a generalized maculopapular eruption that occurs during the second week of treatment and is usually accompanied by pruritus and fever. The incidence of skin rashes to TMP-SMX in healthy subjects is 3% to 5%, whereas reaction rates of 40% to 80% have been reported in patients with HIV.[28] Because TMP-SMX is the drug of choice for a number of HIV-associated infections (most notably prophylaxis and treatment of *Pneumocystis carinii*–induced pneumonia), it is not uncommon for HIV-positive patients with a history of reacting to sulfonamides to require treatment with the antibiotic. Consequently, various induction of drug tolerance procedures have been devised to safely administer TMP-SMX to HIV-positive patients with histories of reacting to the antibiotic.[30] The protocols vary greatly in terms of the starting dose, the incremental increase between doses, the time interval between doses, and the total duration of the desensitization; however, the success rates are comparable. Two studies compared the effectiveness of induction of tolerance versus rechallenge (single dose) in HIV-positive patients with documented reactions to TMP-SMX, and there were no differences in the success rates.[31,32] These results place into question the validity of previously reported induction of tolerance procedures that did not include a control group of patients who received full-dose TMP-SMX.

The N_4 aromatic amine is critical for the development of delayed reactions to sulfonamide antibiotics (through oxidation to hydroxyamines and nitroso compounds), and based on more limited data, the N_1 substituted ring appears to be important for IgE-mediated reactions.[28] Because nonantibiotic sulfonamides lack these structural components, they would not be expected to cross-react with sulfonamide antibiotics. Several clinical studies demonstrated no increased risk of reactions to nonantibiotic sulfonamides in patients with a history of allergy to sulfonamide antibiotics.[33]

Local anesthetics

IgE-mediated reactions to local anesthetics are extremely rare,[34] yet many patients are labeled allergic to all "caines" and denied access to these drugs. Most adverse reactions to local

anesthetics are due to nonallergic factors, such as vasovagal responses; toxic or idiosyncratic reactions caused by inadvertent intravenous epinephrine; or anxiety.[35] Local anesthetics are grouped into benzoate esters and amides. Based on patch testing, there is cross-reactivity among the benzoate esters (which do not cross-react with amides) but not among the amides. It is not known what, if any, relevance this has on immediate-type reactions to local anesthetics. If the reaction history is consistent with a possible type I reaction, skin testing followed by graded challenge tests can be performed with the same (epinephrine-free) local anesthetic that is intended to be used. Although there are differences in reported graded challenge procedures, a rapid and convenient protocol is as follows.[36] Skin prick testing is first performed with the undiluted anesthetic. If the response is negative after 20 minutes, an intradermal test is performed with 0.04 mL of 1:100 dilution of local anesthetic. If the response is negative after 20 minutes, a 1.0-mL subcutaneous injection of saline as a placebo is administered. If there is no reaction after 20 minutes, 1.0 mL of local anesthetic is administered, and the patient is observed for 20 minutes.

False-positive intracutaneous test results can occur in some patients.[37] Also, very rare patients can have positive skin test responses to methylparabens in local anesthetics, and some of these can be false-positive.[36] In these situations preservative-free local anesthetic should be used for skin testing/graded challenge.

Radiocontrast media

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occur in about 1% to 3% of patients who receive ionic radiocontrast media (RCM) and less than 0.5% of patients who receive nonionic agents.[38] Severe life-threatening reactions are less common: 0.22% of patients receiving ionic RCM and 0.04% of patients receiving nonionic agents.[39] The fatality rate from RCM is about 1 to 2 per 100,000 procedures, and it is similar for both ionic and nonionic agents.[40] Risk factors for anaphylactoid reactions to RCM include female sex, asthma, and a history of a previous anaphylactoid reaction to RCM; β-blocker exposure, the presence of cardiovascular conditions, or both are associated with greater risk for more serious anaphylactoid reactions.[41]

The pathogenesis of anaphylactoid reactions is unrelated to "seafood allergy" (attributed to high iodine content); patients with food allergy require no special precautions before receiving RCM. RCM reactions are generally not mediated by specific IgE antibodies. RCM likely has direct effects on mast cells and basophils, leading to degranulation and systemic mediator release, which accounts for the clinical manifestations of anaphylactoid reactions. Complement activation might account for some reactions. A recent European trial suggests that some RCM reactions might be IgE mediated because approximately half of patients with immediate-type reactions to RCM had positive skin test responses, which were highly specific.[42]

Management of patients who require RCM and experienced prior anaphylactoid reactions includes the following: (1) determine whether the study is essential; (2) determine that the patient understands the risks; (3) ensure proper hydration; (4) use a nonionic, iso-osmolar RCM, especially in high-risk patients (asthmatic patients, patients taking β-blockers, and those with cardiovascular disease); and (5) use a pretreatment regimen that has been documented to be successful in preventing most reactions but is less successful in preventing recurrence of severe reactions.[43] Pretreatment is defined as the administration of medications before administration of a drug to lessen the likelihood and severity of a drug-induced allergic reaction. Medications used for pretreatment are thought to be effective because of blockade of receptors for mast cell mediators or through reduction in mast cell mediator release (mast cell stabilization). A typical pretreatment regimen consists of 50 mg of prednisone 13, 7, and 1 hour before the procedure; 50 mg of diphenhydramine 1 hour before the procedure; and either 25 mg of ephedrine or 4 mg of albuterol 1 hour before the procedure. However, the latter agents might not be favorable from a risk/benefit standpoint in patients with cardiovascular disease. The use of H_2 antagonists in the pretreatment regimen is controversial because it can increase the RCM reaction rate.[43]

Delayed reactions to RCM, defined as those occurring between 1 hour and 1 week after administration, occur in approximately 2% of patients.[44] These reactions most commonly manifest as mild, self-limited cutaneous eruptions and do not require any treatment.[44] The mechanism of delayed skin reactions to RCM appears to be T-cell mediated.[45] Rarely, more serious and life-threatening delayed reactions to RCM have been described, such as SJS and TEN.[45]

Anaphylactoid reactions to gadolinium occur less frequently than to contrast materials used for computed tomographic scans.[46] Premedication regimens consisting of corticosteroids and antihistamines have been successfully used.[47] Nephrogenic systemic fibrosis (NSF), also called gadolinium-associated systemic fibrosis, is a recently described devastating progressive systemic fibrosing disorder that afflicts patients with renal dysfunction who recently received gadolinium.[48] The mechanism of NSF has not been elucidated, but it is hypothesized that dechelation of gadolinium chelates attracts $CD34^+$, $CD45^+$, procollagen-positive circulating fibrocytes.[48] Gadolinium has been found in biopsy specimens of skin lesions. Pre-existing renal failure might facilitate the reaction by delaying the excretion of gadolinium chelates. There is no effective treatment for NSF, and affected patients have increased mortality.[48]

Angiotensin-converting enzyme inhibitor: Cough and angioedema

Angiotensin-converting enzyme inhibitors (ACE-Is) have 2 major adverse effects: cough and angioedema. The incidence of cough from ACE-Is ranges from 5% to 35%.[49] Cough occurs more commonly in women, nonsmokers, and Chinese patients. The cause for ACE-I–induced cough is unclear but might be related to bradykinin, substance P, or other mechanisms. ACE-I–induced cough is typically dry and might be associated with a tickling sensation in the throat. The cough can occur within hours of the first dose or within weeks or months of initiation of therapy. With discontinuation of the ACE-I, the cough usually resolves in 1 to 4 weeks and rarely lingers up to 3 months.[49] In patients for whom cessation of ACE-I therapy is not desirable, several pharmacologic agents have been reported in small case series to reduce coughing, including cromolyn, theophylline, NSAIDs, amlodipine, nifedipine, and ferrous sulfate.[49] ACE-I–induced cough is not dose related, and angiotensin II receptor blockers are not associated with an increased incidence of cough.[50]

The incidence of angioedema to ACE-Is is estimated to occur in 1 to 7/1,000 patients, and this risk is higher in African-Americans compared with that seen in whites.[51] ACE-I–induced

TABLE VI. Hypersensitivity reactions to aspirin and NSAIDs and cross-reactivity

Type of reaction	Underlying disease	Cross-reactivity with COX-1 inhibitors
Respiratory (AERD)	Rhinitis, nasal polyps, sinusitis, asthma	Yes
Urticaria/AE	Chronic urticaria	Yes
Urticaria/AE	None	Yes or no
Anaphylaxis	None	No

The cross-reactivity patterns depicted in this table are generally true, but exceptions can occur.
AE, angioedema.

angioedema is often unrecognized because its manifestation can occur anywhere between a few hours to 10 years after an ACE-I is first taken. A recent retrospective study found a mean of 1.8 years from initiation of an ACE-I until the onset of angioedema.[52] ACE-I–induced angioedema accounts for approximately one third of all patients presenting to the emergency department for angioedema.[53] Characteristically, ACE-I–induced angioedema involves the head and neck primarily, especially the lips and tongue; concomitant urticaria and pruritus are rare. In some cases laryngeal edema can cause fatalities. Reports of angioedema of the intestinal tract caused by ACE-Is have also been described. Bradykinin is a prominent mediator in both hereditary angioedema and ACE-I–induced angioedema.[54] ACE-Is are contraindicated in patients with hereditary angioedema. In patients with ACE-I–induced angioedema, angiotensin II receptor blockers are often used as alternative medications. Limited data suggest that in patients with angioedema, when taking an ACE-I, the risk of persistent angioedema when subsequently switched to an angiotensin II receptor blockers is less than 10%.[55] Treatment includes discontinuing the medication and careful management of the airway, and in some cases fresh frozen plasma has been useful.

Acetylsalicylic acid/NSAID reactions

Acetylsalicylic acid (ASA) and NSAIDs can cause a spectrum of drug-induced allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis. Some of these drug-induced allergic reactions exhibit cross-reactivity to other NSAIDs and aspirin, whereas some reactions might be drug specific (Table VI).

Aspirin-exacerbated respiratory disease (AERD) is a clinical entity characterized by ASA/NSAID-induced respiratory reactions in patients with underlying chronic respiratory diseases, such as asthma, rhinitis, sinusitis, and/or nasal polyposis. AERD has been previously referred to by a number of different terms, including aspirin sensitivity, aspirin intolerance, aspirin idiosyncrasy, aspirin-induced asthma, and aspirin or Samter's triad. AERD does not fit precisely into a specific category of ADRs, although it has often been referred to as a type of pseudoallergic reaction. AERD affects up to 20% of adult asthmatic patients, is more common in women, has an average age of onset around the age of 30 years, and usually starts with rhinitis, progressing to hyperplastic sinusitis and nasal polyposis.[56] Asthma might be present since childhood or might develop *de novo*, on average 2 years after the onset of nasal congestion and polyposis.

Fundamental to the pathophysiology of AERD is excessive production of cysteinyl leukotrienes, increased numbers of inflammatory cells expressing cysteinyl leukotriene 1 receptors, and greater airway responsiveness to cysteinyl leukotrienes. In addition, a number of genetic polymorphisms involving the leukotriene pathway have been reported to be associated with AERD, including the leukotriene C_4 promoter, the cysteinyl leukotriene 1 receptor promoter, and prostanoid and thromboxane receptor–related genes.[57] Administration of ASA leads to inhibition of COX-1, with a resultant decrease in prostaglandin E_2 levels. Prostaglandin E_2 normally inhibits 5-lipoxygenase, but with a loss of this modifying effect, arachidonic acid molecules are preferentially metabolized in the 5-lipoxygenase pathway, resulting in increased production of cysteinyl leukotrienes.

Within minutes of ingestion of therapeutic doses of ASA or NSAIDs, patients with AERD typically have both rhinoconjunctivitis and bronchospasm. The bronchospasm induced can be severe and result in respiratory failure with a need for intubation and mechanical ventilation. Gastrointestinal symptoms and urticaria are rare extrapulmonary manifestations of AERD. Patients with AERD will react to ASA and NSAIDs that inhibit COX-1. Selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely.

There is no diagnostic *in vitro* or skin test for AERD. The diagnosis is usually established based on history, but when a definitive diagnosis is required, a controlled oral provocation challenge with ASA can be performed. A recent study showed that 100% of patients with a history of a severe reaction to aspirin (poor response to albuterol with need for medical intervention) had positive oral aspirin challenge esults.[58] Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical, surgical, or both types of treatment of underlying asthma and rhinitis/sinusitis. A pharmacologic induction of drug tolerance procedure (also known as aspirin desensitization), during which tolerance to aspirin can be induced over a few days and then maintained chronically, is an important therapeutic option for patients with AERD and improves clinical outcomes for both upper and lower respiratory tract disease.[59,60]

Several other drug-induced allergic reactions to ASA or NSAIDs can occur. Patients with chronic urticaria/angioedema might have exacerbation of their urticaria/angioedema with ingestion of NSAIDs that inhibit COX-1 but typically tolerate COX-2 inhibitors. Patients without a history of underlying chronic urticaria/angioedema can have acute urticaria/angioedema with ingestion of aspirin or NSAIDs. Some of these patients demonstrate cross-reactivity to other COX-1 inhibitors, whereas others have selective reactions to a particular NSAID. Anaphylactic reactions to NSAIDs are typically drug specific, and these patients typically tolerate other NSAIDs.[61] Finally, some patients are not easily categorized who have blended reactions with overlap of various clinical features from the above well-described ASA/NSAID reaction syndromes.

HIV medications

Patients infected with HIV have an increased frequency of drug-induced allergic reactions, and the reasons behind this are likely multifactorial.[62] Drug exanthems from TMP-SMX are among the most common drug-induced allergic reactions in patients with HIV, as previously discussed. Antiretroviral medications have also been associated with numerous drug-induced allergic reactions, ranging from mild exanthems to life-threatening reactions, such as SJS or TEN.

Although many antiretroviral medications can cause drug-induced allergic reactions, abacavir deserves special mention because of the successful implementation of a pharmacogenetics approach to management. Abacavir is a nucleoside reverse transcriptase inhibitor that is associated with a hypersensitivity reaction in approximately 4% of treated patients, with an estimated mortality rate of 0.03%.[63] This multiorgan reaction includes symptoms such as fever, rash, malaise/fatigue, gastrointestinal symptoms, and respiratory symptoms. In 90% of cases, hypersensitivity reactions occurred within the first 6 weeks after initiation of abacavir. Rechallenge with abacavir resulted in recurrence of symptoms within hours of re-exposure, including hypotension in 25% of those rechallenge reactions. Because of the severity of reactions on rechallenge, hypersensitivity to abacavir is a contraindication to subsequent treatment with any formulation that includes it.

Investigations into genetic risk factors associated with these reactions discovered that several HLA alleles, most notably HLA-B*5701, were strongly associated with risk of abacavir hypersensitivity reactions.[64,65] The prevalence of HLA-B*5701 varies considerably by ethnicity and geography, with estimated US prevalences of 8% for whites, 1% for Asians, and 2.5% for African Americans.[66] A double-blind, prospective, randomized study of 1,956 predominantly white patients with HIV from 19 countries was performed to evaluate the utility of genetic screening before initiation of abacavir therapy.[67] Subjects were randomly assigned to undergo prospective HLA-B*5701 screening with exclusion for abacavir treatment if screened positive. Screening for HLA-B*5701 reduced the risk of hypersensitivity reaction to abacavir, with reaction rates of 3.4% in the screened group versus 7.8% in the control group. A North American study with a more racially diverse population demonstrated that genetic screening decreased the rate of abacavir hypersensitivity to less than 1%, which is lower than historical rates.[68] The ability to identify genetic predispositions to drug-induced allergic reactions and implement genetic screening tests, as in the case of abacavir hypersensitivity, might hold promise for preventing other drug-induced allergic reactions in susceptible persons.[69]

Cancer chemotherapeutic agents

Hypersensitivity reactions have been reported for most cancer chemotherapeutic agents.[70] The severity of reactions can range from mild cutaneous reactions to fatal anaphylactic reactions. Taxanes, such as paclitaxel and docetaxel, can cause anaphylactoid reactions (non–IgE-mediated anaphylaxis), frequently with the first administration. Pretreatment with antihistamines and corticosteroids will prevent reactions in greater than 90% of cases.[71] Platinum compounds, such as cisplatin, carboplatin, and oxaliplatin, typically cause hypersensitivity reactions after several treatment courses. Results of skin testing have been found to be positive in the majority of patients with immediate reactions to platinum-containing compounds, suggesting an IgE-mediated mechanism. Cetuximab is an mAb used to treat colorectal cancer and squamous cell carcinoma of the head and neck and has been associated with anaphylactic reactions. IgE antibodies to cetuximab have been found in the majority of anaphylactic reactions and are specific for an oligosaccharide, galactose-α-1,3 galactose, which is present on the Fab portion of the cetuximab heavy chain.[72] Procedures to induce drug tolerance have been reported to be successful and safe in platinum-containing compounds, taxanes, and other chemotherapeutics.[73]

Biologic modifiers

In the past decade, a number of biologic immune modulatory agents have been developed to treat various inflammatory diseases and tumors. They are comprised of proteins such as cytokines, mAbs, and fusion proteins of solubilized receptors. These agents differ from other drugs in that they are not small-molecular-weight compounds but large potentially immunogenic proteins. Their metabolism is different, many are naturally occurring proteins, and all have inherent immunologic effects. Because of all of these differences, a separate type of classification for adverse reactions to biologic agents has been proposed based on the mechanism of reactions.[74] High-dose reactions are related to high cytokine levels administered directly or from cytokines released (eg, capillary leak syndrome). Hypersensitivity reactions can be either antibody or cell mediated. Immune or cytokine dysregulation can result in secondary immunodeficiency, autoimmunity, or allergic/atopic disorders. Cross-reactive reactions can occur when the biologic agent is intended for a pathologic cell type but cross-reacts with normal cells. Finally, biologic agents can also result in nonimmunologic side effects. Interferons are an example of biologic agents capable of causing most of the above reactions, including high-dose flu-like symptoms, hypersensitivity reactions of urticaria, autoimmune reactions (including thyroid disease and psoriasis), and nonimmunologic effects, such as depression.

Capillary (vascular) leak syndrome is a rare but potentially fatal condition that has been attributed to a number of biologic agents, including IL-2, GM-CSF, and granulocyte colony-stimulating factor.[75] Clinical and biochemical findings can include fever, edema (peripheral, pulmonary, ascites, and pleural/pericardial effusions), weight gain, hypotension, hypoalbuminemia, and multiorgan failure. The mechanism of the endothelial damage with subsequent fluid and protein extravasation is unclear but appears to be related to the inherent biologic effects of these cytokines.

TNF-α antagonists include humanized and fully human mAbs to TNF-α (infliximab and adalimumab) and TNF-receptor fusion proteins (etanercept). Acute infusion reactions are a relatively common adverse reaction to infliximab, often after the first dose, usually occurring within 4 hours of the infusion, and characterized by symptoms including hypotension/hypertension, chest pain, dyspnea, fever, and urticaria/angioedema.[76] The pathophysiology of these reactions is not known but is usually not IgE mediated, although several cases of anaphylaxis have been reported. The majority of patients can continue the infusion with reduction in rate or with premedication.[77] Delayed serum sickness–like reactions with symptoms of fever, urticaria/angioedema, and myalgias have also been reported but are much less common. The presence of antibodies to infliximab has correlated with both acute and delayed infusion reactions to infliximab. Etanercept and, less commonly, adalimumab are associated with delayed injection site reactions that typically peak at 2 days, usually occur in the first 2 months of therapy, and rarely cause discontinuation of treatment. Recall injection site reactions at the sites of previous injections can also occur and can be T-cell mediated delayed-type hypersensitivity reactions.[78] In addition to the above-mentioned infusion- or injection-related reactions, a number of other immunologic adverse reactions have been reported with TNF-α

antagonists, including vasculitis, systemic lupus erythematosus, psoriasis, interstitial lung disease, ocular autoimmune diseases, sarcoidosis, and hepatitis.[79]

Omalizumab is an mAb to human IgE approved for the treatment of asthma. Anaphylactic reactions have been reported with omalizumab in less than 0.1% of treated patients.[80] Most, but clearly not all, anaphylactic reactions occur to the first 3 doses and within 2 hours of the injection.

Finally, although not often considered a biologic therapy, intravenous gamma globulin has been associated with a variety of infusion reactions. The most common infusion-related reactions include symptoms of headache, fever, chills, tachycardia, anxiety, nausea, dyspnea, arthralgia, and myalgias and rarely more serious signs, such as hypotension. Most infusion reactions are mild and rate related and occur 6 to 24 hours after an infusion. The mechanisms causing these reactions are postulated to involve activation of complement by immunoglobulin aggregates, antigen-antibody complexes, and contaminant vasoactive proteins.[81]

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